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Synopsis of Material: This report is a treatment of the fundamental chemistry of cellular respiration for possible presentation at the high school level. This presentation should serve to acquaint the students with the processes involved in cellular respiration and give them a better appreciation and understanding of the complexity of life and perhaps an interest to pursue the field of biological science. The different biochemical processes involved were discussed from photosynthesis in green cells of plants to oxidation within the mitochondria of all cells. The intermediate processes were covered and their significance to the overall process of cellular respiration was stressed. The reactions of glycolysis, Krebs cycle and the cytochrome system were illustrated to facilitate a firmer grasp of the material presented. The emphasis of this report was on the general aspects of the processes involved and no attempt was made to present all the details.

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THE FUNDAMENTAL CHEMISTRY OF
CELLULAR RESPIRATION

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CELLULAR RESPIRATION

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PREFACE

It was the purpose of this report to collect and organize information concerning the fundamental chemistry of cellular respiration which could be presented at the high school level. Commonly the gases, oxygen and carbon dioxide, are involved in respiration and the method by which gaseous exchanges take place is very important. Eventually however, the seat of the basic chemical reactions is within the protoplasm of the living cells of plants and animals. These basic reactions constitute cellular respiration. The emphasis of this report was on the general aspects of the processes involved and no attempt was made to present all the details. Without some understanding of these areas, a person cannot fully appreciate some of the great advances that have been made in modern biology.

One should bear in mind that new contributions are being made in this area continually, and that which may be accepted as facts today, may well be discarded tomorrow to make way for a new and better, and perhaps, more complete explanation. Thus it is obvious that the study and understanding of biochemical processes, in both plants and animals, is a field that is relatively new and is in a state of continual change.

TABLE OF CONTENTS

LIST OF CHARTS

CHAPTER I

INTRODUCTION

Lavoisier in 1779 first conceived of life as oxidation. He lived in an age when the nature of chemical energy and its use in machines was just being clarified. Lavoisier extended these concepts to include both plants and animals. He and Laplace designed experiments to test their energy-conversion postulates. They constructed a calorimeter to determine whether energy exchanges occurred in living things in the same manner as they did in nonliving systems. They placed a guinea pig in a cage and surrounded it with two chambers filled with ice. The outer ice chamber absorbed any heat from the environment. The heat produced by the animal during the experiment was determined by the volume of water produced by the melting ice in the inner chamber. (Gabriel, 1955).

In a parallel experiment, Lavoisier and Laplace determined the amount of food combusted during the course of the experiment by measuring the amount of carbon dioxide the guinea pig produced. They concluded that energy conversion in the animal's body was the same as that which occurred in a nonliving chemical system. (Giese, 1962).

In all living cells, energy to maintain life is given off through oxidation (cellular respiration) of the organic compounds, chiefly carbohydrates. The green cells of plants, containing chlorophyll, can manufacture organic nutrients from inorganic compounds, binding the energy of sunlight in photosynthesis and storing it as potential chemical energy. But cells lacking chlorophyll must depend upon such organic compounds as are made by plants and must be supplied with them as food. Many animals are also dependent upon green plants for vitamins as well. (Giese, 1962).

CHAPTER II

RELATIONSHIP OF PHOTOSYNTHESIS AND RESPIRATION

Photosynthesis is the process by which the green plants convert the energy of light into the stored chemical energy of foods; respiration is the process that converts this stored energy into energy available for the synthesis of fats, proteins, and other organic compounds, for growth, reproduction, movement, active transport, and energy for other physiological processes. Respiration is basically a process of oxidation - that is, it involves the addition of oxygen to, or the removal of hydrogen from, the material undergoing respiration, as a result energy is liberated. The oxygen involved in this oxidative process may be derived from free oxygen in the atmosphere which, dissolved in water, enters the cells of plants, or it may be oxygen that is transferred from one type of chemical compound to another. Respiration is often compared with the burning of wood, etc., which liberates energy stored in these materials in the form of heat and light. This is a very poor comparison, for oxidation in living organisms takes place at slower rates and at lower temperatures than those involved in the combustion of fuels, and is subject to controlling factors unlike those involved in the burning of wood, etc. From the energy released from food by respiration, a portion escapes from the bodies of living organisms as heat; the balance is used to provide the necessary energy for energy-using physiological processes, some of which were previously mentioned. (Fuller, 1963).

Respiration is sometimes defined as the intake of oxygen and the release of carbon dioxide by organisms, or is used to denote "breathing". This usage of the word "respiration" is confusing and misleading. The fundamentally significant feature of respiration is that it is a chemical process that takes place in all living cells. The main characteristic of the process is a chemical reaction of oxidation, not the exchange of oxygen and carbon dioxide, which is incidental to the chemical process itself. The use of the word "respiration" is such terms as "artificial respiration" is physiologically misleading, the word breathing" should be used. (Johnson, 1961).

The respiratory processes vary to some degree in different kinds of organisms, but all types of respiration have certain common characteristics: the chemical breakdown of food, the liberation of energy as a result of this breakdown, transfers of oxygen and hydrogen among foods and other materials involved in respiration, and the production of carbon dioxide. (Giese, 1962).

The knowledge of cellular respiration, the actual dynamics of life, represents and portrays an achievement fully equal to any other in the whole of biological science. It confers on us not only a profound understanding of living processes but also an enlarged area of control over them, in anesthetics, in medicine, in industries concerned with fermentations of various sorts, even in control of the nervous system and animal behavior. One astonishing fact made clear by modern research is that the chief energy-yeilding processes are essentially the same in all organisms. (Moment, 1958).

A summary of the comparison of photosynthesis with respiration may be made in the following manner. Photosynthesis absorbs water and carbon dioxide, liberates oxygen, makes sugar and other compounds, increases the dry weight of tissues, stores energy in foods, proceeds in green cells only, and proceeds only in the presence of light. Respiration releases water and carbon dioxide, absorbs oxygen, breaks down sugar and other compounds, decreases the dry weight of tissues, releases energy stored in foods, proceeds in all living cells, and proceeds in light or darkness.

CHAPTER III

MITOCHONDRIA

Nearly all living cells contain subcellular organelles called mitochondria. These small, rod-shaped or spherical bodies are dispersed in the cytoplasmic ground substance and may occasionally contact the endoplasmic reticulum. Mitochondria are numerous, some investigators estimating as many as 1,000 or more per cell. These cytoplasmic organelles reproduce themselves. Each mitochondrion is bounded externally by a double membrane, the inner layer of which is deeply infolded, forming internal membrane extensions called cristae. The mitochondria play an important part in cellular physiology for they are the principal center of respiratory activity.

During the process of respiration, energy is released by oxidative chemical reactions within the mitochondria where it is immediately transferred to molecules of an energy transporting compound. These molecules in their high-energy state are then moved out of the mitochondria to other parts of the cells where the energy is used to sustain the various life processes. (Brachet, 1961).

The area between the mitochondria consists of a network of membrane bound channels or vacuoles forming the endoplasmic reticulum. On the surface of the reticulum are ribosomes and other microsomal granules. (Zamecnik, 1958).

When mitochondria are separated from the cell (by differential centrifugation) and studied, it is found that they perform all of the reactions of the Krebs cycle, including oxidative phosphorylation. They have, therefore, been named the "powerhouses of the cells". Some evidence has been presented that indicates the reactions characteristic to the Krebs cycle may occur along successive parts of a mitochondrial lamella. (Siekevitz, 1957).

A given enzyme, localized on a spot of the mitochondrial lamella, will presumably attract only its specific substrate. For example, succinic dehydrogenase attracts only succinic acid, causing the transfer of two hydrogen atoms to the flavoprotein carrier, resulting in the formation of fumaric dehydrogenase, etc. The molecule leaves each enzyme in turn to pass to the next enzyme in the chain to which it is now specifically attracted. These reactions continue in this manner until the series is complete. The enzymes which catalyze the anaerobic reactions are apparently located outside the mitochondria. (Green, 1958).

CHAPTER IV

ANAEROBIC RESPIRATION

The overall formula for cellular respiration is: $C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O +$ Energy, but this does not begin to tell the entire story. There are many reactions between the starting glucose and the formation of carbon dioxide and water.

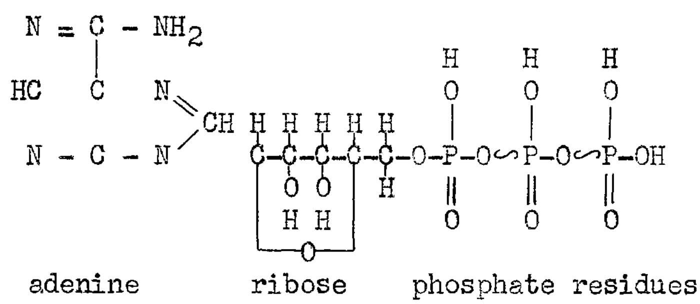
Fermentation and Respiration

In the nineteenth century it was thought that only intact cells could carry on fermentation and respiration, to some investigators this indicated the need for a vital force found only in living protoplasm. However, in free "zymase" filtered from the ground cells was capable of fermenting glucose, forming alcohol and carbon dioxide in a similar manner as did intact yeast cells. (Gabriel, 1955). This indicated that fermentation, and possibly other oxidative activities of cells, are catalyzed by biocatalysts called enzymes, which carry on their activities even in the absence of cells. Since that time many of the enzymes participating in fermentation and in respiration have been isolated and their specific functions in the chain of reaction determined. (Rose, 1960).

Yeast kept in a nutrient solution containing sugar, etc., will ferment the sugar and accumulate alcohol, a fact known far back in history as shown by the great variety of fermented drinks: cider, beer, ale, wine, saki, etc. Yeast, then, can grow and carry on all of its life activities in the absence of oxygen; that is, it is capable of anaerobic existence. (Giese, 1962).

Adenosine Triphosphate (ATP)

Most of the energy released in cells is trapped in the form of chemical bonds. The most important single chemical compound in cells involved in this trapping process is adenosine triphosphate, or ATP. Always associated with ATP in cells is another compound, adenosine diphosphate, or ADP. ATP consists of the nitrogen-containing compound, adenine, linked with the sugar, ribose, and three phosphate groups. (Johnson, 1961). The structure of ATP is given below.



Fritz A. Lipman shared one of the Nobel Prizes in 1953 for his work on the high-energy bonds of ATP. As the formula shows, ATP contains three phosphate groups. The bonds for the two terminal ones are shown as curved (∽) lines while the bond for the first one is shown as a straight (–) line. Breaking one of the terminal bonds by hydrolysis (the chemical decomposition of a substance with water) releases 12,000 calories of energy, while breaking the first bond releases 2,000 to 3,000 calories. Thus the curved line represents a high-energy bond. The straight line represents a low-energy bond. When the terminal phosphate bond of ATP is broken with the release of energy, ADP is formed. ATP may lose energy forming ADP and a phosphate group, but ADP may combine with a phosphate group and energy to form ATP; ATP $\rightleftharpoons$ ADP + phosphate + Energy. (Stumpf, 1953).

ATP and ADP are always present together in cells but only in small amounts. In the overall energy relations in cells, energy is released in certain reactions and in others energy must be added for the reaction to take place. The formation of ATP involves the trapping of most of the energy released in cellular oxidation. In all of the many reactions which require energy - muscle contraction, the synthesis of protein, fats, carbohydrates, of nucleic acids, etc., nerve conduction, kidney functions, bioluminescence, and many others - ATP supplies the energy. The primary role of cellular respiration, therefore, is that of generating high-energy phosphate bonds and of synthesizing ATP. (Giese, 1962).

Glycolysis

The first stages in the oxidation of glucose, leading to the formation of pyruvic acid, are referred to as glycolysis or the anaerobic phase of respiration. This phase is also often referred to as fermentation. In this phase of respiration no oxygen is involved and some microorganisms, (obligatory anaerobes) have only this type of respiration.

In the series of steps down to pyruvic acid a number of different kinds of reactions occur, including phosphorylation, dehydrogenation, and the rearrangement of atoms in the molecules involved. Each reaction is catalyzed by a specific enzyme. (Green, 1958).

Carbohydrates other than glucose may be the starting material in the cell for glycolysis, but glucose may well be considered here.

At first, the glucose molecule combines with a phosphate group furnished by ATP forming glucose-6-phosphate. This is phosphorylation and the glucose molecule is now activated. The energy that is transferred activates the glucose so that it will undergo the series of breakdown changes that follows. The next reaction involves a rearrangement of atoms and fructose-6-phosphate is formed. Next, another phosphate group supplied by ATP is added to fructose-6-phosphate forming fructose-1,6-diphosphate. This molecule is then split into two 3-carbon compounds (the triose phosphates) dihydroxyacetone phosphate and glyceraldehyde-3-phosphate. Only the latter compound is involved in the energy releasing reactions since dihydroxyacetone phosphate is converted into glyceraldehyde-3-phosphate, and from here on there are two triose molecules to follow. In the next reaction each triose molecule reacts with phosphoric acid to form 1,3-diphosphoglyceric acid. In this reaction (dehydrogenation) hydrogen is lost to a hydrogen acceptor and the bond of the second phosphate group becomes a high-energy bond. Up to this point no molecules of ATP have been formed. But in the next reaction the high-energy phosphate group is transferred to ADP and ATP plus 3-phosphoglyceric acid are formed. Since two molecules were involved, two molecules of ATP are produced. This replaces the two ATP molecules used in the earlier reactions. In the next reaction the remaining phosphate group is shifted to the middle carbon atom forming 2-phosphoglyceric acid. Then a molecule of water is removed from this compound forming phosphoenol pyruvic acid with a high-energy phosphate bond. In the final reaction in this series this high-energy phosphate bond is transferred to ADP forming ATP and pyruvic acid. Two molecules of ATP are formed since two molecules of phosphoenol pyruvic acid were involved. This represents the net gain of energy for the functions of the cell in the reactions down to pyruvic acid. (Giese, 1962).

In the formation of 1,3-diphosphoglyceric acid, two hydrogens were released per molecule giving a total of four hydrogens. These were picked up by hydrogen acceptors. In cells that carry on aerobic respiration these hydrogens are ultimately passed through the cytochrome system (to be discussed later) to form water in this process of terminal oxidation. However, in anaerobic cells, (as certain bacteria), in yeast cells under anaerobic condition, and in muscle cells during strenuous exercise when oxygen is not present, this can not happen. In these situations pyruvic acid serves as the final hydrogen acceptor. When hydrogen is transferred to pyruvic acid, lactic acid is formed in certain bacteria and in the muscles of animals, and alcohol and carbon dioxide are formed in yeast cells. Under aerobic conditions pyruvic acid is oxidized in a series of reactions called the Kreb's or citric acid cycle. (Lehninger, 1960).

CHAPTER V

AEROBIC RESPIRATION

Kreb's Cycle

In the series of reactions in the Krebs Cycle pyruvic acid is broken down into carbon dioxide and hydrogen which later unites with oxygen to form water. Citric acid is formed from oxaloacetic acid and at the end of the cycle, oxaloacetic acid appears again.

Hans A. Krebs first demonstrated the nature and significance of this cycle in 1947, and shared one of the Nobel Prizes in 1953 for his work.

Even when oxygen is present, the first steps in the breakdown of the glucose molecule to form pyruvic acid in the cell are the same as in its absence (glycolysis). At the start of the Krebs cycle, the pyruvic acid undergoes a decarboxylation with the removal of carbon dioxide, forming a 2-carbon fragment called acetyl. This fragment joins with coenzyme A (CoA) forming acetyl-CoA. In these reactions water is added and two hydrogens are liberated. The acetyl fragment combines with the 4-carbon oxaloacetic acid and CoA is freed, producing citric acid, a 6-carbon compound. Then, through a series of reactions, cisaconitic acid, isocitric acid, oxalosuccinic acid, alpha-ketoglutaric acid, succinic acid, fumaric acid, and malic acid are produced, leading finally to the starting compound, oxaloacetic acid. These reactions that produce the above compounds involve the removal of carbon dioxide (decarboxylation), and the removal of hydrogen atoms (dehydrogenation). In following two molecules of pyruvic acid (the result of one molecule of glucose) through the cycle it is seen that six molecules of carbon dioxide are formed (three for each acetyl fragment) plus the release of twenty hydrogen atoms (five pairs for each acetyl fragment). These twenty hydrogen atoms plus the four released during glycolysis unite with twelve atoms of oxygen to form twelve molecules of water in the cytochrome system. (Giese, 1962).

Cytochrome System

The hydrogen atoms released in the Krebs cycle, just as the hydrogen released in glycolysis, are taken up by hydrogen acceptors. The most important coenzymes which function as the first acceptors of hydrogen are diphosphopyridine nucleotide (DPN), and triphosphopyridine nucleotide (TPN). In some reactions one functions, and in other reactions the other functions. When DPN unites with hydrogen, it reduces DPN to give DPN•2H. The same process occurs when hydrogen unites with TPN to form reduced TPN or TPN•2H. In aerobic respiration the reduced pyridine nucleotide may release its hydrogens to a flavoprotein, a second hydrogen carrier in the series. If this happens, the reduced pyridine nucleotide is oxidized and the flavoprotein is reduced. Next the flavoprotein passes its hydrogens to the first of a series of cytochromes, iron-containing compounds (cell pigments) which form the cytochrome system. (Kamen, 1958). Four cytochromes (B, C, A, and A_3) pass the hydrogens successively down the series. The last cytochrome, (A_3) called cytochrome oxidase, passes the hydrogens to oxygen, activating it. The activated oxygen, acting as the hydrogen acceptor, combines with the free hydrogen to form water. (Baldwin, 1957). In each of the oxidation-reduction reactions energy is released and trapped in the form of ATP molecules.

CHAPTER VI

RELATIONSHIP OF AEROBIC AND ANAEROBIC RESPIRATION

Anaerobic respiration is apparently of general occurrence in all living cells. In many lower organisms, such as yeast and some bacteria, anaerobic respiration is the only type of respiration normally carried on, these organisms, called anaerobes, commonly live in the absence of free oxygen. Most higher plants respire anaerobically for a time, at least, if they are deprived of oxygen. When higher plants are deprived of oxygen for a few hours, their tissues develop small amounts of some intermediate products (acetaldehyde, for an example) of anaerobic respiration. Also, when seedlings in air are given fermented sugar solutions, their respiration rate increases, indicating they can respire products of alcoholic fermentation. Although higher plants may respire anaerobically, they can live normally only in the presence of free oxygen. (Fuller, 1963).

CHAPTER VII

SUMMARY AND CONCLUSIONS

Summary

As stated before, at the end of glycolysis, there is a net gain of two ATP molecules. Thus at the end of glycolysis, over 90% of the energy of the original molecule of glucose is still in the two molecules of the pyruvic acid formed. It is estimated that the energy released during the aerobic phases of respiration results in the formation of thirty-eight additional molecules of ATP for each molecule of glucose. Thus, much more ATP is formed in the aerobic phase. These thirty-eight molecules of ATP plus the two formed during glycolysis (40 total) would constitute the total net energy trapped in the overall process. Complete combustion of one molecule of glucose releases approximately 673,000 calories. This gives an efficiency factor of about 70% for the overall process which is very high when compared to the steam engine and diesel engine which is about 25% and about 40% efficient respectively. (Rose, 1960).

Although the oxidation of glucose was considered here under the topics of glycolysis, Krebs cycle, and the cytochrome system, it is important to realize that they are not really separate; but function continuously and simultaneously in the living cell. Also, the path for the degradation of glucose, as treated here, is a basic one to be found in many kinds of cells, many modifications of parts of it have been found in the diverse kinds of cells that have been studied. (Moment, 1958).

Conclusions

Cellular respiration is a topic which is not normally encountered until a student reaches college. It is a subject which, by its very nature, is complex even in its most basic form. This is especially true for students in high school when one considers that these students generally aren't exposed to organic chemistry to any great extent, if at all. However, this writer feels that the basic material contained in this report can be arranged and modified for presentation at the high school level. This presentation would serve to acquaint the students with the processes involved in cellular respiration and give them a better appreciation and understanding of the complexity of life and perhaps an interest to pursue the field of biological sciences.

CHART I

GLYCOLYSIS

GLUCOSE (6C)

ATP

ADP

GLUCOSE-6-PHOSPHATE (6C)

ATP

ADP

FRUCTOSE-6-PHOSPHATE (6C)

FRUCTOSE-1,6-DIPHOSPHATE (6C)

GLYCERALDEHYDE-3-PHOSPHATE (3C) X2

1,3-DIPHOSPHOGLYCERIC ACID (3C) X2

ATP X2 (4 H)

3 PHOSPHOGLYCERIC ACID (3C) X2

2 PHOSPHOGLYCERIC ACID (3C) X2

H_2O

PHOSPHOENOL PYRUVIC ACID (3C) X2

ADP

to form ATP X2

PYRUVIC ACID (3C) X2

under anaerobic conditions pyruvic acid may move in two different directions

under aerobic conditions pyruvic acid is passed to Krebs cycle (see CHART II)

by bacteria, animal muscle, etc.

LACTIC ACID (3C)

by yeast

ALCOHOL (2C) & CO_2

CHART II

KREBS CYCLE

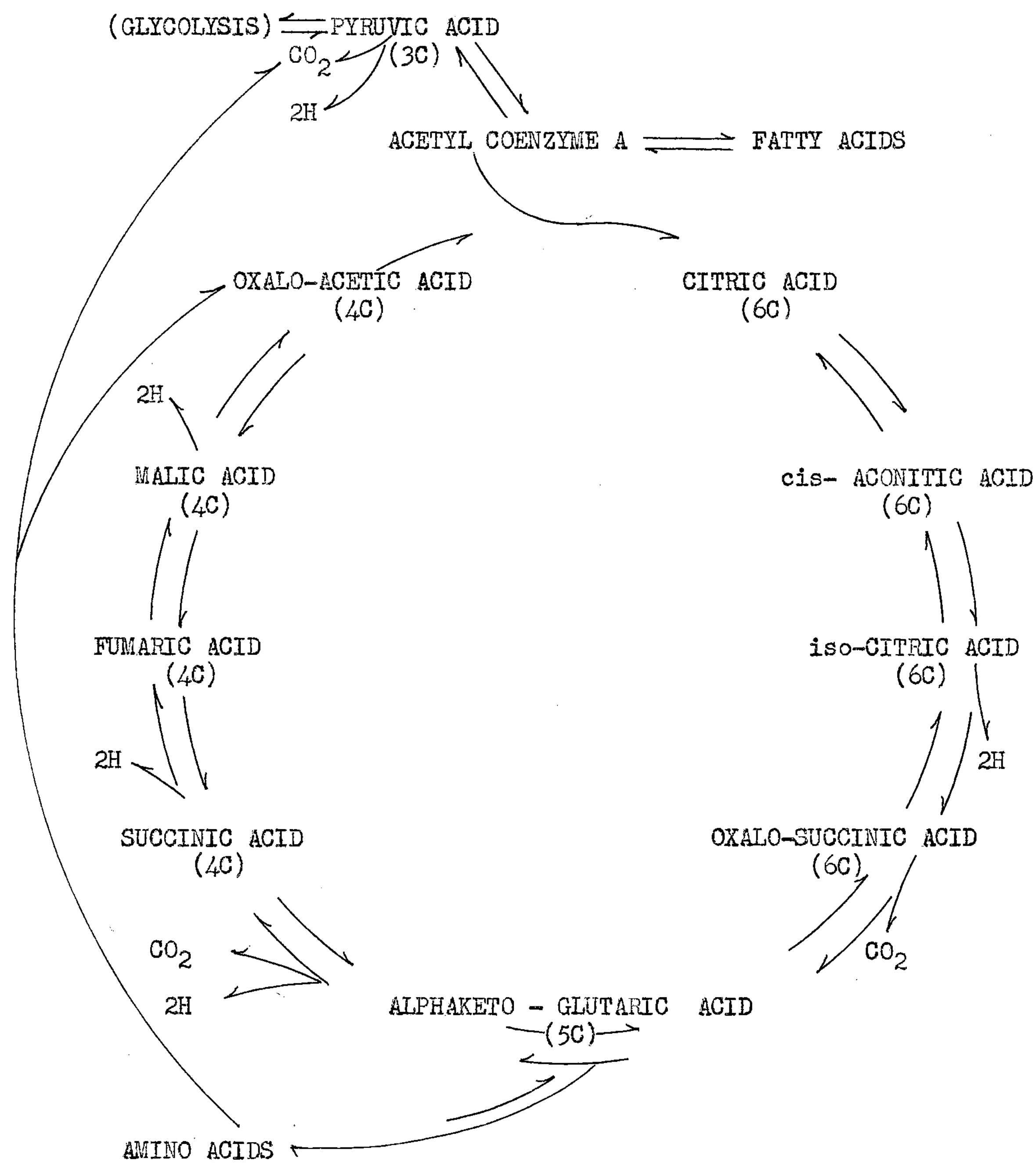
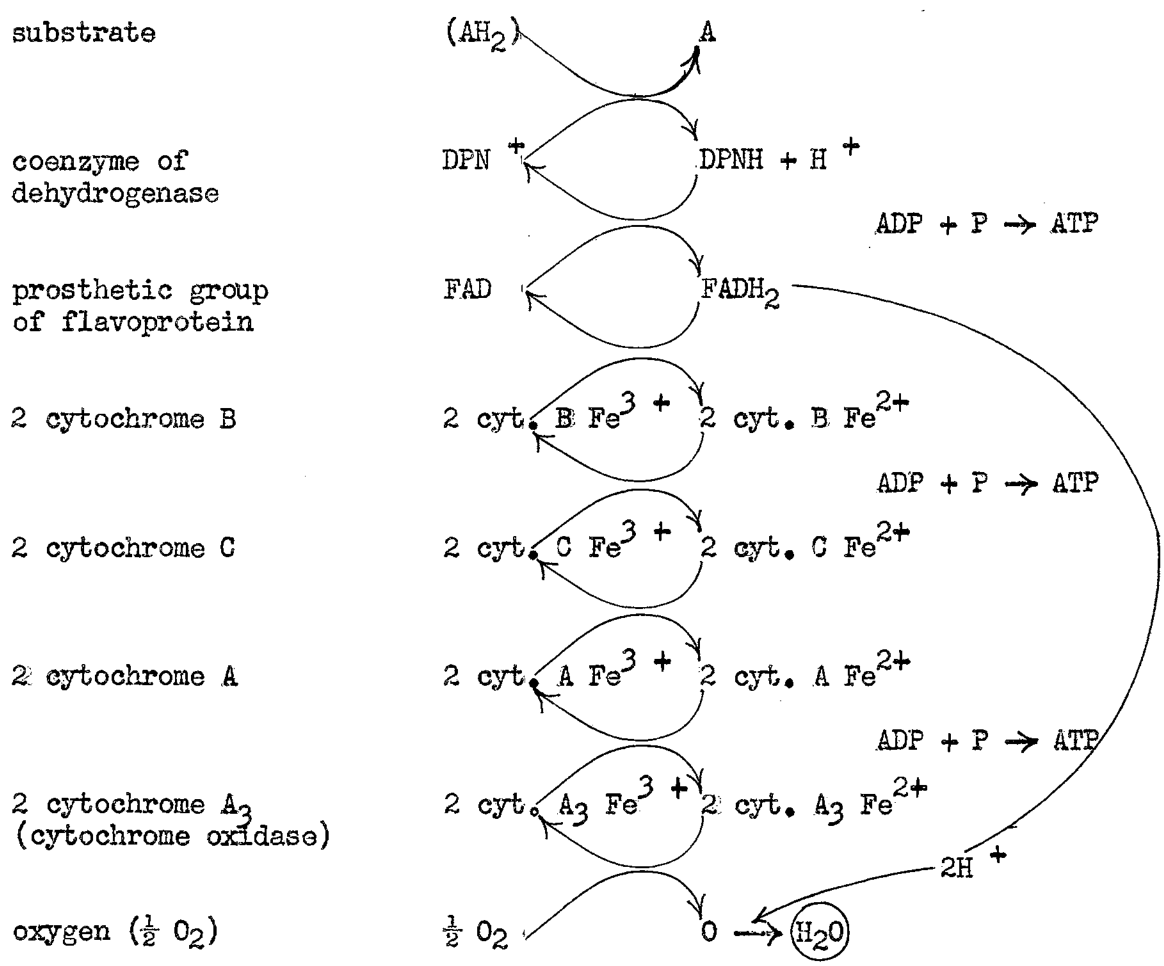


CHART III

CYTOCHROME SYSTEM



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